



A Case of Suspected Cardiac Amyloidosis: A Diagnostic Challenge in a 22-Year-Old Male with Restrictive Cardiomyopathy

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ABSTRACT

Introduction

Cardiac amyloidosis (CA) is a progressive and often terminal infiltrative cardiomyopathy resulting from the extracellular deposition of misfolded protein fibrils—primarily immunoglobulin light chains (AL) or transthyretin (ATTR)—within the heart muscle. While historically perceived as a rare condition affecting the elderly, advances in non-invasive imaging have revealed CA as an underdiagnosed cause of heart failure. However, its manifestation in young adults remains exceptionally rare, presenting a significant diagnostic challenge for general practitioners. Early recognition is vital, as subtype-specific therapies can significantly alter the clinical trajectory.

Case Illustration

We report the case of a 22-year-old male who presented with a two-week history of progressive dyspnea, orthopnea, abdominal distention, and periorbital edema. Physical examination revealed signs of systemic congestion, including ascites (shifting dullness) and decreased breath sounds in the right lung, alongside a blood pressure of 130/90 mmHg and a heart rate of 94 bpm. Laboratory findings were remarkable for a severely elevated NT-proBNP of 8177.11 pg/mL and a high hemoglobin of 18.2 g/dL. Chest radiography demonstrated cardiomegaly (CTR 63%), pulmonary edema, and bilateral pleural effusion. Electrocardiography (ECG) revealed low-voltage QRS complexes, which stood in stark contrast to the echocardiographic evidence of significant ventricular wall thickening (IV S 1.27 cm, LV PW 1.83 cm,) and a reduced ejection fraction of 35.3%. The discordance between ECG voltage and echocardiographic mass, combined with Grade III diastolic dysfunction, strongly suggested cardiac amyloidosis.

Discussion

The diagnostic hallmark in this case is the "voltage-to-mass" discordance, a pathognomonic red flag where amyloid fibrils insulate the myocardium, dampening electrical signals despite increased wall thickness. In a 22-year-old, the differential diagnosis includes hereditary transthyretin amyloidosis (vATTR) or immunoglobulin light chain (AL) amyloidosis, alongside mimickers like sarcoidosis or Fabry disease. The elevated NT-proBNP and high hemoglobin reflect severe hemodynamic stress and potential hemoconcentration. Management involved stabilizing heart failure using loop diuretics and transitioning to guideline-directed medical therapy (GDMT), while pursuing definitive subtyping through serum/urine immunofixation and

cardiac imaging.

Conclusion

This case emphasizes that cardiac amyloidosis must be considered in young patients presenting with unexplained heart failure and restrictive physiology. Maintaining a high index of suspicion for "red flags" like ECG-echo discordance is essential to facilitate early diagnosis and initiation of life-saving, subtype-specific treatments.

Keywords

amyloidosis, cardiac amyloidosis, restrictive cardiomyopathy, heart failure, young adult, NT-proBNP

INTRODUCTION

Cardiac amyloidosis (CA) represents one of the most complex and rapidly evolving frontiers in modern cardiology. It is defined as a clinical syndrome resulting from the extracellular deposition of insoluble, β -pleated protein fibrils within the myocardial interstitium, which leads to the disruption of cardiac architecture, progressive stiffening of the ventricles, and ultimately, a terminal state of restrictive cardiomyopathy.¹ Although the term "amyloid" was first coined by German botanist Matthias Schleiden in 1838 and later introduced to human pathology by Rudolph Virchow, our understanding of the disease as a treatable condition has only solidified within the last decade.⁴

Historically, the incidence of cardiac amyloidosis was thought to be negligible, often confined to post-mortem findings in the very elderly.⁴ However, contemporary epidemiological data suggests a dramatic shift. Population-based autopsy studies have indicated that cardiac amyloid deposition may be present in up to 25% of individuals aged over 80 years.⁴ The UK National Amyloidosis Center database reported a 670% increase in diagnosed cases between 1987 and 2019, a trend largely attributed to increased clinical awareness and the development of sophisticated non-invasive diagnostic modalities such as technetium-labeled bone scintigraphy and cardiac magnetic resonance (CMR) imaging.⁴

The vast majority of clinical cardiac amyloidosis cases (>95%) are caused by one of two precursor proteins: immunoglobulin light chains (AL amyloidosis) or transthyretin (ATTR amyloidosis).² AL amyloidosis is a plasma cell dyscrasia wherein an abnormal clone of B-cells in the bone marrow produces misfolded kappa or lambda light chains. This form is considered a medical emergency due to its aggressive nature and the direct proteotoxicity of the light chains, which cause rapid cardiomyocyte death and severe diastolic dysfunction.⁸ ATTR amyloidosis involves the transthyretin protein, a liver-synthesized transporter for thyroxine and retinol-binding protein.¹¹ ATTR can manifest in two forms: wild-type (wtATTR), an age-related stability failure of the protein, and hereditary or variant (vATTR), caused by over 130 possible genetic mutations in

the TTR gene.¹¹

The clinical presentation of cardiac amyloidosis is notoriously non-specific, often masquerading as common hypertensive heart disease or heart failure with preserved ejection fraction (HFpEF).⁶ This diagnostic mimicry often leads to significant delays in treatment, with studies suggesting that nearly 37% of patients are not correctly diagnosed until a year after their initial symptoms.¹⁷ In young adults, the diagnostic challenge is even more profound. While wtATTR is a disease of the elderly, AL amyloidosis and certain vATTR mutations, such as the Val30Met variant, can appear in patients as young as their second or third decade of life.¹⁴

Feature	AL Amyloidosis	ATTR Amyloidosis (Wild-type)	ATTR Amyloidosis (Variant/Hereditary)
Precursor Protein	Immunoglobulin Light Chain	Transthyretin (Normal)	Transthyretin (Mutated)
Origin	Bone Marrow (Plasma Cells)	Liver	Liver
Typical Age	50 – 70 years	> 65 years	Varies (can be < 30 years)
Progression	Rapid (Months)	Moderate (Years)	Moderate (Years)
Organ Involvement	Multi-system (Heart, Kidney, Nerve, GI)	Primarily Heart, Tendons	Heart and/or Nerves
Prognosis (Untreated)	Median < 6 months if heart failure	3 – 5 years	Varies by mutation

Early diagnosis is critical because the therapeutic landscape has transformed from purely supportive care to highly specific, disease-modifying interventions. For AL amyloidosis, intensive chemotherapy and stem cell transplantation can induce hematological remission.²¹ For ATTR, novel stabilizers like Tafamidis and gene silencers like Vutrisiran have been proven to reduce mortality and improve quality of life.¹¹ This report details the clinical journey of a 22-year-old male presenting with hallmark signs of cardiac amyloidosis, highlighting the diagnostic "red flags" that remain indispensable for general practitioners and specialists alike.

CASE ILLUSTRATION

Patient History and Narrative

The patient, identified as L.A.S., a 22-year-old male, was admitted to the hospital with a primary complaint of shortness of breath that had progressively worsened over a two-week period. He described the dyspnea as being particularly severe when lying flat (orthopnea), which significantly impeded his ability to sleep. Approximately one week prior to admission, he noticed his abdomen becoming increasingly distended and firm. Furthermore, he reported recurrent swelling around his eyes (periorbital edema) that was most prominent upon waking in the morning.

Review of systems revealed a persistent cough with occasional productive phlegm, but the patient denied fever, chest pain, nausea, vomiting, or gastrointestinal disturbances such as diarrhea. His urinary output remained subjective normal, though he noted some generalized fatigue. His social history was remarkable for occasional alcohol consumption several times per week; however, he denied any tobacco or illicit drug use. There was no documented prior history of hypertension, diabetes, or similar symptoms in his family.

Physical Examination Findings

Upon initial assessment in the emergency department, the patient appeared moderately distressed and tachypneic. His consciousness was clear (GCS E4V5M6). The physical examination provided several critical clues toward a systemic infiltrative process.

Parameter	Value/Finding	Clinical Interpretation
Blood Pressure	130/90 mmHG	Normal to high-normal; lack of hypotension
Heart Rate	94 bpm	Regular; no tachycardia at rest
Respiratory Rate	24x/minute	Tachypneic; sign of pulmonary congestion
Temperature	36,2°C	Afebrile
Oxygen Saturation	98% (Room Air)	Preserved at rest
Head/Neck	Periorbital edema (+/+)	Suggests systemic fluid overload or renal loss
Lungs	Decreased vesicular BS (Right)	Suggests right-sided pleural effusion
Heart	Single S1, S2; no murmurs	No valvular disease detected initially
Abdomen	Distended; Shifting dullness (+)	Ascites; sign of right-sided heart failure
Extremities	Warm acral; No leg edema	Fluid sequestered in abdomen/pleura

The absence of significant lower extremity edema despite the presence of ascites and periorbital edema is an unusual finding in traditional congestive heart failure but can occur in infiltrative diseases where fluid distribution is affected by altered oncotic pressures or localized capillary leak.

Laboratory Investigations

A comprehensive laboratory workup was performed to evaluate hematological, metabolic, and cardiac status. The results revealed profound elevations in cardiac wall stress markers and unusual hematological parameters.

Test	Result	Unit	Reference Range
Hematology			
Hemoglobin (Hb)	18.2	g/dL	13.5 – 18.0
Hematocrit (Hct)	51.9	%	40.0 – 54.0
WBC	8.54	$10^3/\mu\text{L}$	4.50 – 11.00
Platelets	209	$10^3/\mu\text{L}$	150 – 440
Chemistry			
GDS (Random Glucose)	117	mg/dL	< 170
Urea	26	mg/dL	13 – 43
Creatinine	0.73	mg/dL	0.67 – 1.17
Albumin	3.60	g/dL	3.50 – 5.20
Electrolytes			
Sodium (Na ⁺)	131	mmol/L	136 – 145
Potassium (K ⁺)	3.9	mmol/L	3.5 – 5.1

Chloride (Cl-)	106	mmol/L	97 – 111
Cardiac/Thyroid			
NT-proBNP	8177.11	pg/mL	< 125
Free T4	2.07	ng/dL	0.70 – 1.48
TSHS	4.775	μIU/mL	0.35 – 4.94

The NT-proBNP level (> 8000 pg/mL) is extremely high and serves as a powerful prognostic marker in cardiac amyloidosis, correlating with the degree of myocardial infiltration. The elevated hemoglobin (18.2 g/dl) and mild hyponatremia (131 mmol/L) may reflect a state of hemoconcentration and severe neurohormonal activation common in advanced heart failure.

Diagnostic Imaging and Electrical Assessment

Electrocardiography (ECG)

The 12-lead ECG demonstrated a regular sinus rhythm with a notable finding: low-voltage QRS complexes in the limb leads. This is defined by a QRS amplitude of < 5 mm in all limb leads. No significant ST-T wave changes or conduction blocks were initially identified, though poor R-wave progression was suspected.

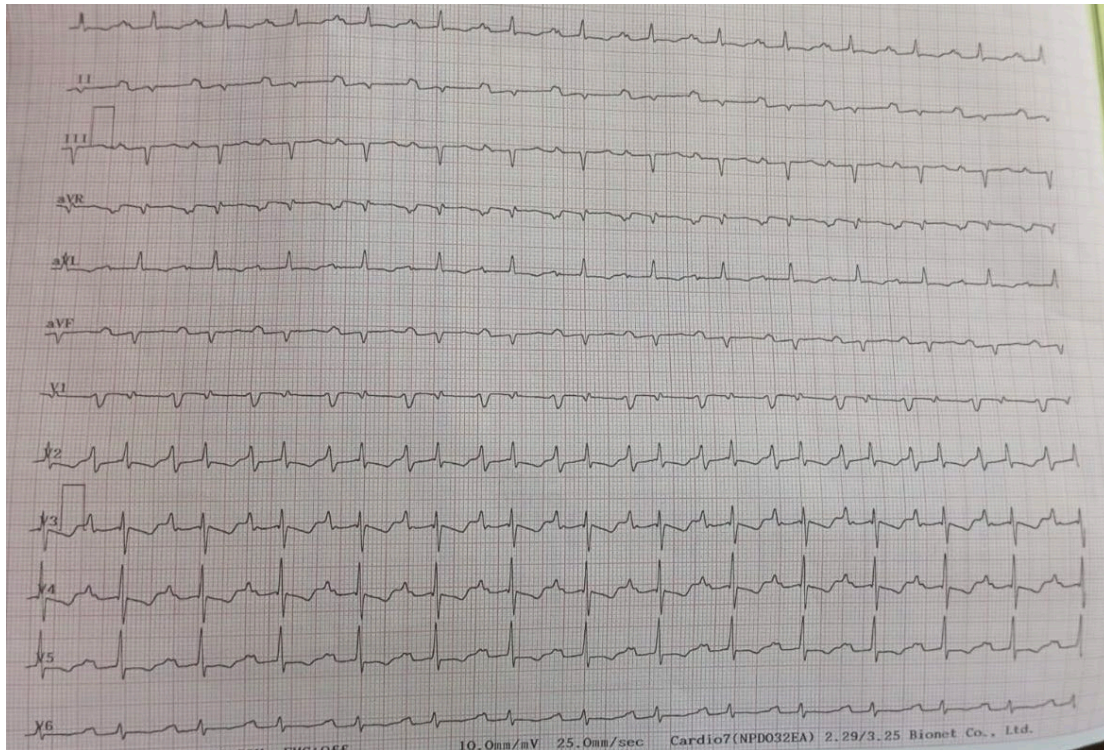


Figure 1. Electrocardiography (ECG)

Thoracic Radiography

Chest X-ray (AP view) confirmed the clinical suspicion of severe congestive heart failure.

- **Heart:** Cardiomegaly was present with a Cardiothoracic Ratio (CTR) of 63%.
- **Lungs:** There were visible infiltrates in both lung fields, along with pulmonary edema and bilateral pleural effusions (indicated by blunted costophrenic angles).

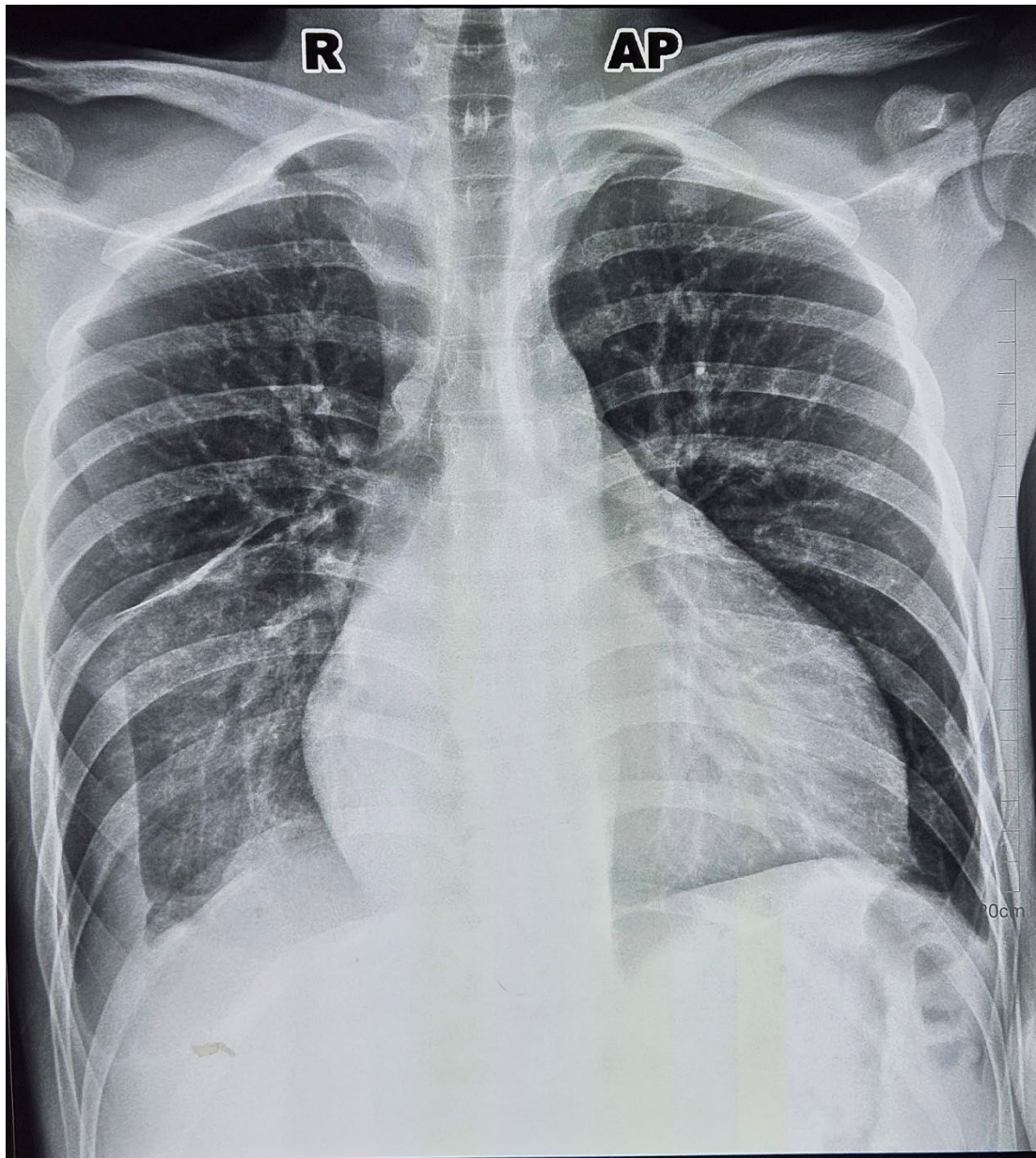


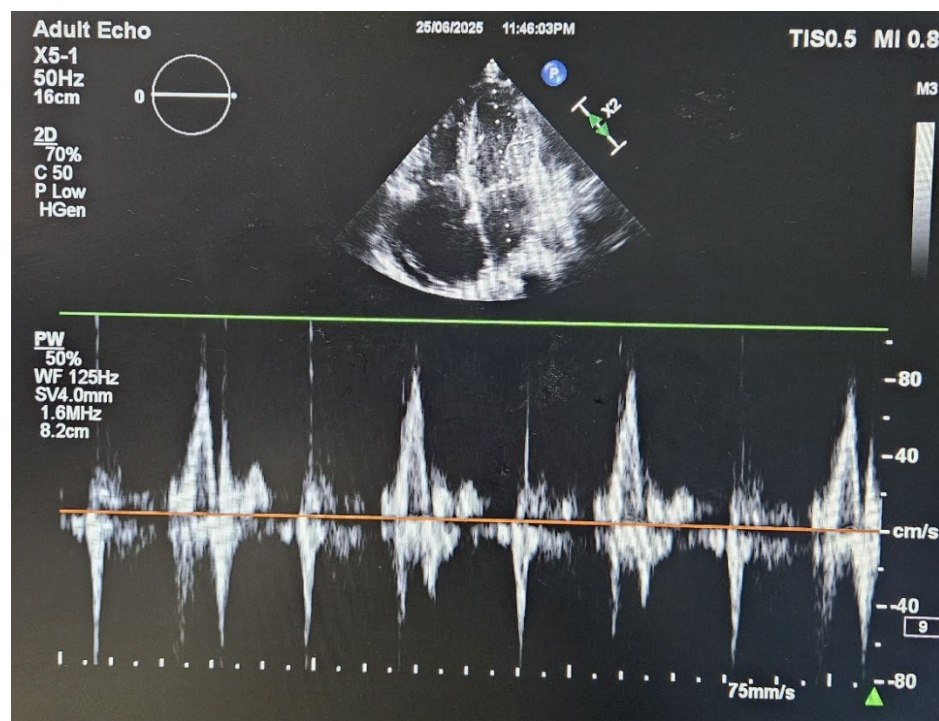
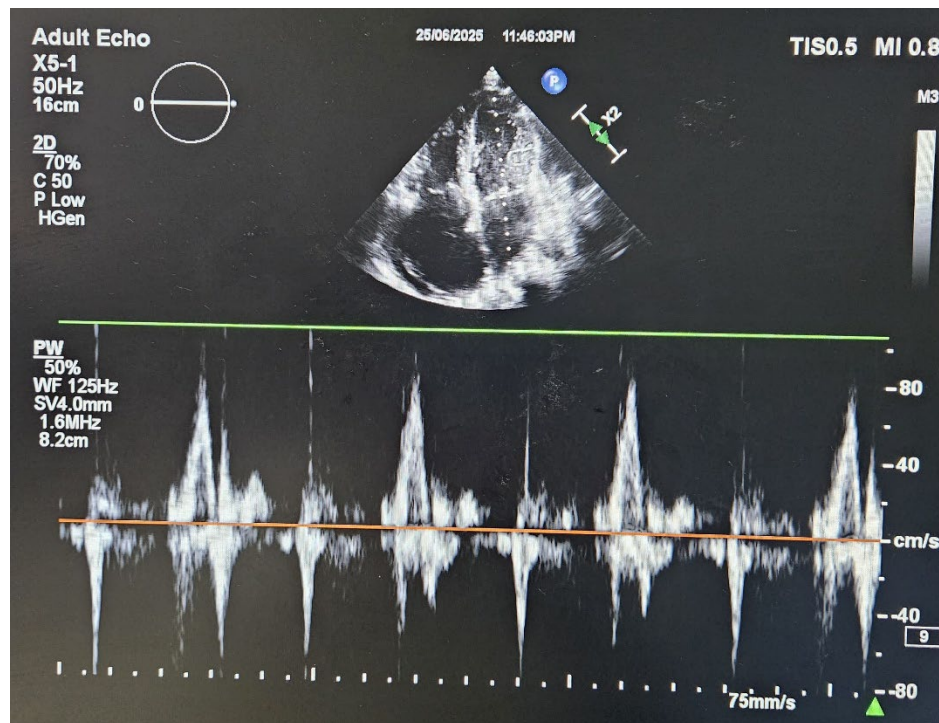
Figure 2. Thoracic Radiography

Echocardiography

The transthoracic echocardiogram (TTE) provided the definitive evidence for a restrictive/infiltrative pathology.

Parameter	Measured Value	Significance
LV Ejection Fraction	35.3%	Moderately reduced systolic function
Interventricular Septum (IVS)	1.27 cm	Thickened/Hypertrophied
LV Posterior Wall (LVPW)	1.83 cm	Significant thickening/Hypertrophy
LV Diastolic Function	Grade III	Restrictive filling pattern
LVIDd	3.43 cm	Small to normal cavity size
Tricuspid Regurgitation	Moderate	Secondary to high filling pressures
Mitral Regurgitation	Mild	Secondary to atrial enlargement
Pericardial Effusion	Mild	Common in amyloidosis

The discordance between the increased wall thickness on echo (> 12 mm) and the low voltage on ECG is a "red flag" with high specificity for cardiac amyloidosis.



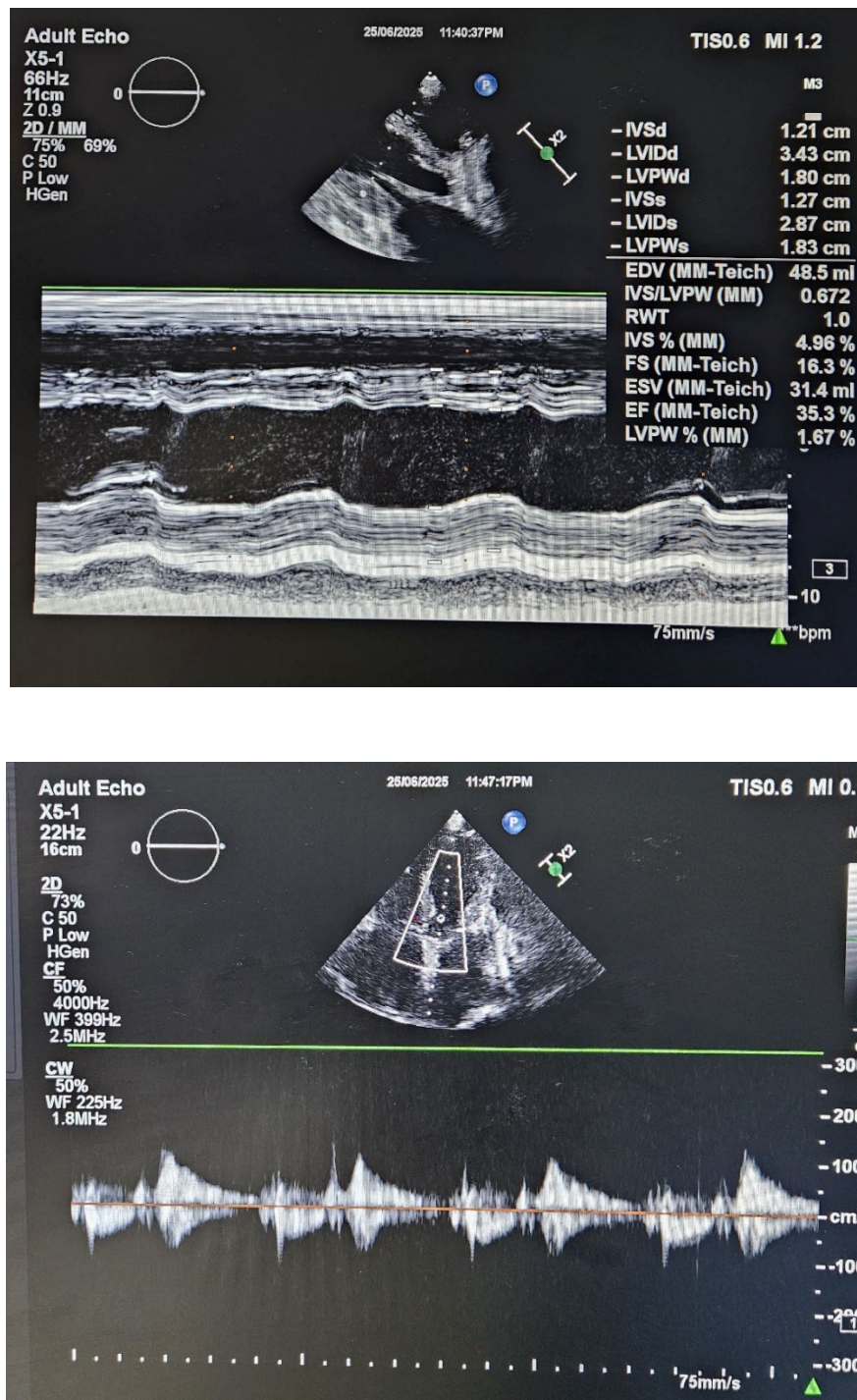


Figure 3. Echocardiography

Initial Diagnosis and Therapeutic Management

The clinical diagnosis was formulated as Congestive Heart Failure (NYHA Class III) with reduced ejection fraction (35%), secondary to an Infiltrative Cardiomyopathy—highly suspected to be Cardiac Amyloidosis, given the constellation of restrictive physiology, ECG-echo discordance, and systemic edema.

Initial inpatient management included:

- **Diuretic Therapy:** Intravenous Furosemide (40 mg every 12 hours) and oral Spironolactone (25 mg) were initiated to manage the ascites and pleural effusions.
- **GDMT Stabilization:** After initial stabilization and improvement in congestion, the patient was started on a low-dose ACE inhibitor (Ramipril 2.5 mg) and transitioned to Sacubitril/Valsartan (2 x 50 mg) upon discharge.
- **Infection Control:** Due to the cough and lung infiltrates, intravenous Cefoperazone (2 x 1 gr) was administered.
- **Long-term Planning:** The patient was referred for advanced diagnostic testing, including serum free light chain assays and cardiac MRI, to confirm the amyloid subtype and determine eligibility for targeted therapies.

DISCUSSION

Pathophysiological Insights: The Mechanism of Infiltration

The hallmark of cardiac amyloidosis is the infiltration of the myocardial interstitium by misfolded protein fibrils, a process that fundamentally alters both the mechanical and electrical properties of the heart.² These fibrils are not merely inert deposits; they are the product of a complex failure in protein homeostasis.¹⁰

In the case of transthyretin (ATTR) amyloidosis, the pathology begins in the liver, where the TTR protein is synthesized as a stable tetramer.¹¹ In disease states, this tetramer dissociates into

monomers that are prone to misfolding. Once these monomers aggregate into fibrils, they deposit between myocytes, leading to "pressure atrophy" of the adjacent cardiac cells.⁴ In hereditary variants, which are highly relevant given our patient's young age, single amino acid substitutions (like the Val30Met or Val122Ile mutations) decrease the kinetic stability of the tetramer, accelerating this process.¹³

In immunoglobulin light chain (AL) amyloidosis, the pathogenesis involves a clonal population of plasma cells.¹⁹ These cells secrete an excess of unstable monoclonal light chains that circulate in the blood and eventually target the heart.¹⁰ A critical insight in AL-CA is the concept of **proteotoxicity**. Soluble pre-fibrillar light chains have been shown to directly induce oxidative stress and mitochondrial dysfunction in cardiomyocytes, often leading to severe heart failure even before massive amyloid deposition is visible on imaging.³ This may explain the rapid progression and very high NT-proBNP levels seen in this patient.⁹

The Pathognomonic Red Flag: ECG-Echo Discordance

One of the most profound clinical features in this case is the discordance between the electrical activity of the heart and its physical mass.³⁴ Traditionally, when a patient presents with thickened ventricular walls (hypertrophy), the ECG shows large QRS voltages because there is more muscle mass to generate electrical current. However, in cardiac amyloidosis, the "thickening" is not due to myocyte hypertrophy but to the accumulation of amyloid fibrils.⁴

Mechanism	Description	Effect on Diagnosis
Insulation Effect	Amyloid fibrils are non-conductive and act as an electrical insulator. ³⁴	Dampens the QRS signal, leading to low voltage. ³⁵
Infiltration vs. Hypertrophy	Deposits expand the interstitium, pushing myocytes apart. ⁴	Thick walls on Echo, but fewer active myocytes for ECG. ³⁶

Pseudo-infarction	Fibril deposition in the septum can mimic old scar tissue. ³⁴	Leads to poor R-wave progression in precordial leads. ³³
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This "voltage-to-mass" discordance is highlighted in the 2022 and 2024 heart failure guidelines as a primary trigger for further amyloid investigation.⁶ In our 22-year-old patient, the interventricular septum was 1.27 cm and the posterior wall was 1.83 cm, yet the ECG showed low voltage. This finding essentially rules out simple hypertensive heart disease or athlete's heart and makes a primary infiltrative disease the most likely diagnosis.¹⁶

Differential Diagnosis in the Young Adult

While cardiac amyloidosis is the leading suspicion, it is extremely rare in a 22-year-old. Several other conditions must be considered, as their treatments differ significantly.

1. **Cardiac Sarcoidosis:** This is an inflammatory granulomatous disease that can present in younger patients.⁴² Like amyloidosis, it causes wall thickening and heart failure, but it is more likely to present with high-grade atrioventricular (AV) blocks and patchy enhancement on cardiac MRI.⁴²
2. **Hypertrophic Cardiomyopathy (HCM):** This is a genetic disease of the sarcomere and the most common cause of sudden cardiac death in the young.⁴⁸ However, HCM patients usually have very *high* QRS voltage on ECG and their EF is typically supranormal (> 70%) rather than reduced (35.3%).³⁶
3. **Fabry Disease:** A rare X-linked lysosomal storage disorder.⁴⁷ It can present with LVH and restrictive physiology in the second or third decade of life. It is often distinguished by extra-cardiac signs such as skin rashes (angiokeratomas) and renal involvement.⁴⁷
4. **Hemochromatosis:** Iron overload can lead to restrictive cardiomyopathy.¹⁶ However, our patient did not have the characteristic "bronze" skin or elevated liver enzymes typical of this condition.

Analysis of Biomarkers: NT-proBNP and Hemoglobin

The NT-proBNP of 8177 pg/mL is a critical finding. In cardiac amyloidosis, NT-proBNP

levels are often "disproportionately" elevated compared to the severity of the patient's symptoms.² This is because the amyloid fibrils cause direct mechanical stress on the myocyte membranes and stimulate the continuous release of natriuretic peptides.¹⁰ Furthermore, NT-proBNP is a cornerstone of the Mayo Staging System, where a level > 1800 pg/mL is associated with significantly reduced survival.²

The high hemoglobin (18.2 g/dL) is less common in heart failure, where anemia is more typical due to chronic inflammation or renal dysfunction.⁵² In this case, it likely represents a state of hemoconcentration.³¹ As fluid leaks from the vascular space into the abdomen (ascites) and periorbital tissues, the remaining blood becomes more concentrated, raising the Hb and Hct levels.³² This is a sign of severe systemic congestion and third-spacing.³¹

Another notable finding was the thyroid panel. The patient had an elevated Free T4 (2.07 ng/dL) but a normal TSHS (4.775 μ IU/mL). Transthyretin (TTR) is the primary carrier for thyroxine (T4) in the blood.¹¹ In patients with TTR abnormalities (either due to misfolding or genetic mutations), the transport and binding of T4 can be disrupted, leading to unusual thyroid function tests even in the absence of clinical thyroid disease.¹¹ This further supports a diagnosis of TTR-related amyloidosis.

Diagnostic Algorithms: The 2024 ESC/AHA Pathway

The current 2024 guidelines emphasize a three-step non-invasive diagnostic pathway for suspected cardiac amyloidosis.⁷

1. **Screen for Monoclonal Protein:** This is the most critical first step. One must perform serum protein immunofixation, urine protein immunofixation, and the serum free light chain (sFLC) assay.⁷ If *any* of these are positive, the patient is suspected of AL amyloidosis and requires an urgent bone marrow or organ biopsy.⁸
2. **Bone Scintigraphy:** If the monoclonal screen is negative, the patient undergoes a technetium pyrophosphate (PYP) or DPD scan.⁷ A positive scan (Grade 2 or 3 cardiac uptake) is

diagnostic of ATTR-CA.⁷

3. **Genetic Testing:** Once ATTR is confirmed, sequencing of the TTR gene is mandatory to determine if the disease is wild-type or hereditary.⁶

In our 22-year-old patient, the discovery of a TTR mutation would be highly likely if ATTR is confirmed.¹³ Conversely, the presence of periorbital edema and massive NT-proBNP elevation strongly warrants a meticulous screen for monoclonal proteins to rule out AL amyloidosis.¹⁹

The Evolving Therapeutic Landscape

Historically, CA was considered a death sentence with no effective treatments. However, 2024 marks a "paradigm shift" in management.³⁷

Heart Failure Management

The standard "quadruple therapy" for heart failure (Beta-blockers, ACE inhibitors, MRAs, and SGLT2i) must be tailored for amyloid patients.³⁸

- **Beta-blockers:** Often poorly tolerated in CA because the heart is stiff and dependent on heart rate to maintain output.³⁵ However, they may be used in low doses for rate control in atrial fibrillation.³⁷
- **ACEi/ARBs/ARNIs:** Can cause severe hypotension in amyloidosis due to autonomic dysfunction.¹⁹ In our case, the patient was started on Sacubitril/Valsartan (Uperio), which requires close blood pressure monitoring.
- **SGLT2 inhibitors:** Recent observational data from 2024 suggests that SGLT2i are safe and provide prognostic benefit in CA patients, despite their exclusion from initial trials.²⁹

Disease-Modifying Therapies

- **TTR Stabilizers (Tafamidis, Acoramidis):** These drugs "lock" the TTR tetramer, preventing fibril formation.⁷ Tafamidis is currently the gold standard for ATTR-CM.¹¹
- **Gene Silencers (Vutrisiran, Patisiran):** These utilize RNA interference to stop the liver from

producing TTR altogether.⁸ They are particularly effective for hereditary ATTR with neurological involvement.¹³

- **Anti-plasma cell therapy:** For AL amyloidosis, the combination of Daratumumab and chemotherapy (CyBorD) is the first-line treatment, aiming for a "very good partial response" (VGPR) to stop further light chain production.²³

Prognostic Considerations

The prognosis for our patient is guarded. NT-proBNP > 8000 pg/mL and an EF of 35% are markers of advanced disease.⁹ In AL amyloidosis, untreated survival is often less than 6 months from the onset of heart failure.⁸ In ATTR, the survival is longer (3-5 years) but is heavily influenced by the specific genetic mutation.¹¹ The 2024 AL-International Staging System (AL-ISS) would likely classify this patient as Stage IIb or IIc, the most high-risk categories.³⁰

CONCLUSION

Cardiac amyloidosis is a clinical chameleon that requires a high degree of suspicion, particularly when it presents in an atypical demographic such as a 22-year-old male. This case illustrates the critical utility of the "voltage-to-mass" discordance—a pathognomonic red flag that should prompt an immediate and structured diagnostic workup. The presence of restrictive Grade III diastolic dysfunction, massive NT-proBNP elevation, and systemic edema in the absence of a long-standing history of hypertension is deeply concerning for an infiltrative pathology.

For general practitioners, the recognition of these "red flags" is the first and most vital step toward saving the patient's life. While advanced subtyping and targeted therapies like Tafamidis or Daratumumab are often administered in tertiary centers, the initial diagnosis and stabilization of heart failure occur in the community and general hospitals. The rapid evolution of the therapeutic landscape means that a timely diagnosis now offers the hope of halting disease progression and significantly improving survival.

In conclusion, cardiac amyloidosis should no longer be viewed as a rare disease of the elderly, but as a critical differential diagnosis in any patient with unexplained heart failure and thickened ventricular walls. Early referral for monoclonal protein screening and specialized cardiac imaging is essential to ensure that patients can access the life-saving therapies that are now available in the 2024 clinical era.

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